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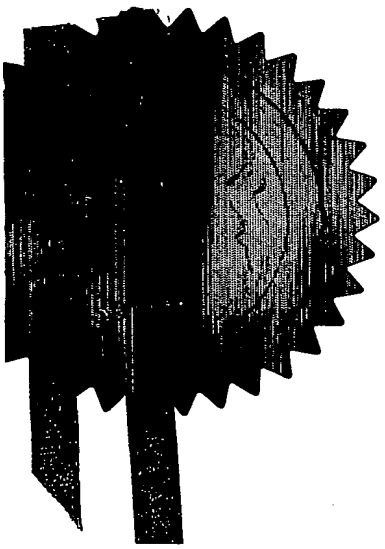

Signed M Conkie

Dated 5 April 2004

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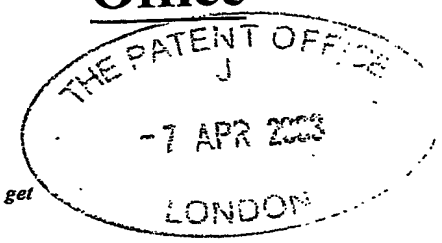

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1. Your reference — -7 APR 2003 — JNR/HG/PB60179P

2. Patent application number
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0307999.3
08APR03 E798397-1 D01030
P01/7700 0.00-0307999.3

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Glaxo Group Limited
Glaxo Wellcome House, Berkeley Avenue,
Greenford, Middlesex UB6 0NN, Great Britain

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation — United Kingdom

4735870003

4. Title of the invention — A System

5. Name of your agent *(if you have one)*

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GlaxoSmithKline
Corporate Intellectual Property (CN9 25.1)
980 Great West Road
BRENTFORD
Middlesex TW8 9GS

Patents ADP number *(if you know it)*

7960982003

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Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

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a) any applicant named in part 3 is not an inventor, or
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Patents Form 1/77

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Continuation sheets of this form	
Description	15
Claim(s)	3
Abstract	1
Drawings	2

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Priority Documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. We request the grant of a patent on the basis of this application

Signature J N Rice Date 7-Apr-03

12. Name and daytime telephone number of person to contact in the United Kingdom: J N Rice 01279 644508

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A SYSTEM

Field of the Invention

The present invention relates to a system comprising a microfluidic chip, and to methods performed on the system.

Background of the Invention

The use of microfluidic chip-based systems is now well established in a variety of disciplines, including analytical chemistry, drug discovery, diagnostics, combinatorial synthesis and biotechnology. Such systems also have important applications where sample volumes may be low, as might be the case in the synthesis or screening of combinatorial libraries, in post-genomic characterisations etc..

The microfluidic chips of such systems have a microfluidic channel structure of small dimension in which the flow rates of liquids therein are relatively high. This leads to faster and cheaper analysis within a smaller footprint. A characteristic effect observed in the microfluidic channel structure is the inherently low Reynolds Number ($Re<700$) which gives rise to laminar flow of the liquid. This effect can be most clearly seen when two flowing streams, from different channels, meet to traverse along a single

channel, resulting in the streams flowing side-by-side. The net result of this phenomenon is that there is no turbulence and mass transfer between the two streams takes place by diffusion of molecules across the interfacial boundary layer. The diffusional mixing across this interface can be fast, with times for mixing ranging from milliseconds to seconds. The diffusion mixing time is even shorter if there is reactivity between the flow streams

Summary of the Invention

According to the present invention there is provided a system comprising a microfluidic chip having a microfluidic channel structure in which fluid reagents are flowable to react to produce a reaction product, and an automated closed-loop control mechanism to autonomously control a condition in, or of, the channel structure in accordance with a prescribed regime, the control mechanism having:-

a sensor adapted to produce a sensor signal representative of a predetermined property of the reaction product which is dependent on the condition in, or of, the channel structure,

means adapted to vary the condition in, or of, the channel structure, and

a computer which is programmed with the prescribed regime and adapted to receive the sensor signal and to cause the means to vary the condition

in, or of, the channel structure in dependence of the sensor signal.

The sensor of the system may form a part of the chip, or be separate therefrom. Preferably, if the sensor is a separate element from the chip, the system has an automated transfer mechanism for transferring the reaction product therebetween.

The sensor of the system may be one of a plurality of different sensors of the system, each sensing a different property of the reaction product. The computer then varies the condition taking account of all of the independent sensor signals.

The closed-loop control mechanism of the system may be adapted to autonomously control a plurality of different conditions in, or of, the channel structure. These conditions may be varied in dependence of sensor signals from a single sensor or from a plurality of sensors. In one case, each condition may be varied in dependence of a different sensor in a sensor array of the system.

The means may be adapted to vary a physical condition in the channel structure, e.g. temperature, pressure, flow rate etc.

The means may be adapted to vary a chemical condition of the reaction product, for example its chemical composition or pH.

The means may be adapted to vary a chemical condition in the channel structure, such as electropheretic movement of ions in the channel structure through electrodes introduced in the channel structure.

The channel structure may have a reaction channel and more than two inlets thereto, at least one inlet being located downstream of one of the other inlets, and the means to vary is adapted to be controlled by the computer to vary the sequence of introduction of the reagents into the reaction channel through the inlets in dependence of the sensor signal. The sequence may be varied by varying the relative timings of the introductions or the relative flow rates through the inlets, or by changing the inlets through which the reagents are introduced into the reaction channel, i.e. swapping the inlets for the reagents around.

Other preferred features of the invention are set forth in the sub-claims and the description of exemplary embodiments which now follows.

Brief Description of the Drawings

FIGURE 1 is a schematic, fragmentary plan view of a microfluidic chip showing its microfluidic channel structure.

FIGURE 2 is a schematic, block diagram of a system of the invention.

FIGURE 3 is a schematic, fragmentary plan view of the microfluidic chip, but with another microfluidic channel structure.

Detailed Description of the Drawings

In the following description, like reference numerals are used to denote like features in the different embodiments.

In FIGURE 1 there is schematically shown a typical microfluidic chip 1 having a Y-shaped microfluidic channel structure 3 provided in an external chip surface 5. The chip 1 is formed from silicon, silica or glass and the channel is provided therein by wet (chemical) or dry (e.g. plasma) etching, as known in the art.

The channel structure 3 has a pair of inlet branch channels 7,9 for the concurrent introduction of two reagents A,B into a common flow channel 11. The channels 7,9,11 are of dimensions which will enable them to sustain a low Reynolds Number with laminar

flow therein (Re<700, preferably Re<10). To this end, the channels are preferably of a width W of no more than 300 microns. The depth of the channels 7,9,11 is preferably no more than the width, and more preferably less than the width by 50% or more (i.e. an aspect ratio of width-to-depth of at least 2:1).

The low Reynolds Number in the channel structure 3 results in the reagents A,B flowing laminarly in the common flow channel 11 in parallel or side-by-side flow streams 13,15, as shown in the inset of FIGURE 1. The net result of this phenomenon is that there is no turbulence and mass transfer between the two flow streams 13,15 takes place by diffusion of molecules across the interfacial boundary layer 17.

The free interface diffusion between the flow streams 13,15 results in mixing of the reagents and the development of a series of "reaction domains" 19 forming in the common flow channel 11, which may be of different colour, for example. This effect can be enhanced by the provision of a mixer at the point of coincidence of the inlet branch channels 7,9.

The reaction domains 19 contain different reaction products and correspond to the different stages of the complete reaction of the reagents A,B. In other words, a time resolution of the reaction of A and B is able to observed in the common flow channel 11. This is due to the different residence times of

the reaction domains 19 in the common flow channel 11. In other words, at a given point in time the leading domain 19a has had a longer residence in the common flow channel 11 than the trailing domain 19b. Thus, the interfacial diffusion between the flow streams 13,15 in the leading domain 19a will have progressed farther than in the trailing domain 19b.

This reaction can be carried out in two different modes. In Mode I, a continuous flow of reagents A,B mix at the point of coincidence of inlet branch channels 7,9 and retain a steady state in the common flow channel 11 such that the reaction domains 19 appear to be stationary therein. In Mode II, on the other hand, discrete plugs of reagents A,B of short duration are released in the respective inlet branch channels 7,9 into continuous non-reacting solvent flow streams and react in a heterogeneous manner in the common flow channel 11, as in Mode I, but fail to retain the steady state achieved in Mode I.

As an example of steady state Mode I, consider the case where reagent A is aqueous potassium permanganate and reagent B is an alkaline aqueous ethanol solution. The reaction domains 19 are of different colour and represent the stepwise reduction of the potassium permanganate with the alkaline ethanol. More particularly, the purple colour of a permanganate (MnO_4^-) domain is changed via a blue

reaction domain to a green reaction domain on the formation of the manganate (MnO_2^-). Depending on the flow rate in the common flow channel 11, additional yellow or brown reaction domains may appear due to the time resolution of manganese dioxide (MnO_2).

As an example of Mode II, a plug of aryl phosphonium bromide (reagent A) is released into a non-reacting continuous flow stream in one of the inlet branch channels 7 (e.g. ethanol) while a plug of a mixture of aryl aldehyde and a base, e.g. sodium methoxide, (reagent B) is released into a non-reacting continuous flow stream (e.g. ethanol) in the other inlet branch channel 9. This results in a heterogeneous reaction in the common flow channel 11 which emits a plug of the stilbene reaction product.

As will be appreciated, the inlet branch channels 7,9 could form a T-shape with the common flow channel 11 instead of the Y-shape.

A computer-controlled system 20 of the present invention incorporating the microfluidic chip 1 is shown schematically in FIGURE 2. The system is controlled by a computer 21 which is operatively coupled to the microfluidic chip 1. The computer 21 is of a standard PC format running a Windows® operating system (Microsoft) with a Pentium® 4 processor (Intel).

The system 20 further comprises a reagent library 23, which may have only two reagents or a greater number of reagents, depending on the process to be carried out on the system 20. Where the reagent library 23 contains a large number of different reagents, the library may take the form of a categorised reagent array, such as available from Caliper Technologies Corporation under the trademark "LibraryCard".

The reagent library 23 is operatively coupled to the microfluidic chip 1 through a transfer mechanism 25. Where only two reagents are to be used, this simplistically takes the form of capillaries extending from the reagents to the inlet branch channels 7,9 of the chip 1. Where a large library of reagents is used, however, as in the case of the categorised reagent array, the transfer mechanism may take the form of a small volume dispensing device, for example the 'sipper chip' available from Caliper Technologies Corporation.

Finally, the system 20 has a sensor 27 for sensing a predetermined property of the reaction product formed in the common flow channel 11 of the chip 1. The sensor 27 may take on various forms, such as passive or interventative, depending on the intended operation of the system 20, as will be

understood hereinafter. The sensor may form a part of the chip 1.

The sensor 27 produces sensor signals 29 which are representative of the predetermined property of the reaction product and feeds these back to the computer 21 for processing thereof.

The computer 21 is programmed with an algorithm to cause the system 20 to operate to produce, or attempt to produce, an optimisation of reaction conditions in the common flow channel 11, or a reaction product in the common flow channel 11 in which the predetermined property is sensed by the sensor 27, or is sensed to be of a predetermined value.

In this regard, the computer 21 and sensor 27 form an automated closed-loop control (or feedback-loop control) of the system 20. By way of explanation, the sensor signal 29 is processed by the computer 21 and results in a demand signal 31 being output by the algorithm which accounts for the sensor signal 29. The demand signal 31 is used to cause a change in a condition in and/or of the chip channel structure 3. More particularly, the demand signal 31 may be used to vary the conditions experienced by the reagents in the chip channel structure 3, for instance flow rate, temperature, pressure, .. etc. Alternatively, or additionally, the demand signal 31 may be used to

change one or more of the reagents transferred from the library 23 to the microfluidic chip 1. In the latter case, the method of selecting a replacement reagent will be determined by the categorisation applied to the reaction array, which categorisation will be programmed in the computer 21.

The system 20 is thus able to "intelligently" and heuristically vary the parameters of the reaction in the chip 1 so as to seek to obtain the goal of the algorithm, e.g. an optimisation of a property of the reaction product. To this end, the algorithm may be a Simplex algorithm or a genetic algorithm or a combination thereof. Instead of, or as well as, an algorithm, a neural network could be used.

Various Examples of the use of the system 20 will now be given.

Example 1 - Chemical Sensor

In this Example, the system is used to optimise a chemical property of the reaction product, e.g. the yield of a specific reaction product in the reaction of reagents A and B, the relative amounts of time-resolved reaction domains, or the amount of a particular isomer.

In this case, the sensor 27 takes the form of a chemical sensor, e.g. a passive sensor such as an

imaging apparatus. When the sensor signal 29 indicates that the yield of the reaction product is not at the set point level in the algorithm, the demand signal 31 is fed either to the transfer mechanism, to vary the flow rate of the reagents for example, and/or to the chip 1 (which in this instance includes any associated equipment for controlling the ambient conditions of the chip 1) to cause a change to another condition in the channel structure 3, e.g. the temperature, etc.

Where several reaction products are being monitored simultaneously in the common flow channel 11, these can be discriminated from one another by determining their molecular weight with mass spectroscopy. This applies generally to the operation of the system 20.

Alternatively, or additionally, the library 23 includes the same reagents, but in different concentrations etc. The demand signal 31 causes the transfer mechanism 25 to vary the reagent combination input to the chip 1.

Example 2 - Biosensor

In this Example the system 20 is used to run a variety of different reagent combinations through the chip 1 and to pass the reaction products through one or more biosensors to test for their possible use in

pharmaceutical applications, e.g. drug discovery. In other words, the system 20 is used for high throughput screening (HTS). Here the closed-loop control operates to find a reaction product from the reagent library 23 for further investigation for pharmaceutical application.

The biosensor(s) may comprise a bioassay and a detector for detecting the interaction of the reaction product with the bioassay and outputting the sensor signal 29. In this regard, the bioassay may be bead-based, and may comprise a plurality of different bioassay beads, and the detector may comprise an imaging apparatus or other type of optical radiation detector.

The system 20 operates to vary the reagent combination input to the chip 1 in response to the sensor signals 29 representative of the preceding reaction product to optimise the reaction product vis-à-vis the biosensor(s). The selection of the "new" reagent by the computer 21 is based on the categorisation of the reagents in the reagent library 23 (see above).

Example 3

In this Example, the chip 1 of the system 20 has the channel structure 103 schematically shown in FIGURE 3. The channel structure 103 has the inlet

branch channel 107 for reagent A and the inlet branch channel 109 for reagent B which in this case is offset (downstream) from inlet branch channel 107. The channel structure 103 further has one or more additional inlet branch channels 125 for another reagent C. Each inlet branch channel 107,109,125 has a valve 130 so as to be independently operable. Again, laminar flow streams are produced in the common flow channel 111.

In this way, the reaction products in selected reactions domains (19, FIG. 1) can be reacted with the reagent C by synchronizing the opening of the inlet branch channel(s) 125 with apposition of the selected reaction domain therewith. Selectivity of a reaction domain for reaction with the new reagent C is assisted by having a series of inlet branch channels 125 (shown in ghost in FIG. 3) so that the time-resolved reaction domains 19 are not "lost" before passing one of the inlet branch channels 125 for reagent C.

Thus, the closed-loop control can operate to vary the time-resolved reaction domain 19 that reacts with reagent C to optimise the reaction product vis-à-vis the sensor 27, or to vary the dwell time of a particular reaction domain before it is reacted with reagent C. In this way, the optimal point of entry of reagent C is found.

Moreover, an inlet arrangement of the sort shown in FIGURE 3 enables the order of mixing of a plurality of reagents to be varied by the system 20 by enabling the computer 21 to cause the reagents (e.g. A-C) to be input through different inlet branch channels 107,109,125 in each new cycle thereof. In other words, the inlets used for the reagents are swapped around to find the optimal arrangement.

It will be understood that the present invention is not limited to the specific embodiments hereinabove described, but may take on may other guises, forms and modifications within the scope of the appended claims. As an example, the system may pass the reaction product through more than one sensor for determination of one than one property thereof and the computer operates to vary the condition in or of the channel structure in response to all of the sensor signals, e.g. to seek to maximise certain reaction product properties while minimising others.

Claims

1. A system comprising a microfluidic chip having a microfluidic channel structure in which fluid reagents are flowable to react to produce a reaction product, and an automated closed-loop control mechanism to autonomously control a condition in, or of, the channel structure in accordance with a prescribed regime, the control mechanism having:-

a sensor adapted to produce a sensor signal representative of a predetermined property of the reaction product which is dependent on the condition in, or of, the channel structure,

means adapted to vary the condition in, or of, the channel structure, and

a computer which is programmed with the prescribed regime and adapted to receive the sensor signal and to cause the means to vary the condition in, or of, the channel structure in dependence of the sensor signal.

2. The system of claim 1, wherein the sensor is a chemical sensor adapted to produce a sensor signal representative of a predetermined chemical property of the reaction product.

3. The system of claim 1, wherein the sensor is a biosensor adapted to produce a sensor signal representative of a predetermined biological property of the reaction product.

4. The system of any one of the preceding claims, wherein the means is adapted to vary a physical condition in the channel structure.

5. The system of any one of the preceding claims having a transfer mechanism to transfer the reagents from a library of reagents to the channel structure.

6. The system of claim 5 in which the operation of the transfer mechanism is controlled by the computer.

7. The system of claim 5 or 6 further including the library.

8. The system of claim 5, 6 or 7, wherein the means to vary the condition in the channel structure is the transfer mechanism, the computer being adapted to cause the transfer mechanism to change the reagent combination in the channel structure in dependence of the sensor signal.

9. The system of any one of claims 1 to 3, wherein the channel structure has a reaction channel and more than two inlets thereto, at least one inlet being located downstream of one of the other inlets, and the means to vary is adapted to be controlled by the computer to vary the sequence of introduction of the reagents into the reaction channel through the inlets in dependence of the sensor signal.

10. The system of any one of the preceding claims whose operation is fully automated.

11. A method of high throughput screening (HTS) of chemical compounds implemented on the system of any one of claims 1 to 10.

12. A method of optimising a predetermined property of a reaction product implemented on the system of any one of claims 1 to 10.

13. A method of screening a compound library for a reaction product having a predetermined property which satisfies a minimum threshold implemented on the system of any one of claims 1 to 10.

ABSTRACT

A System

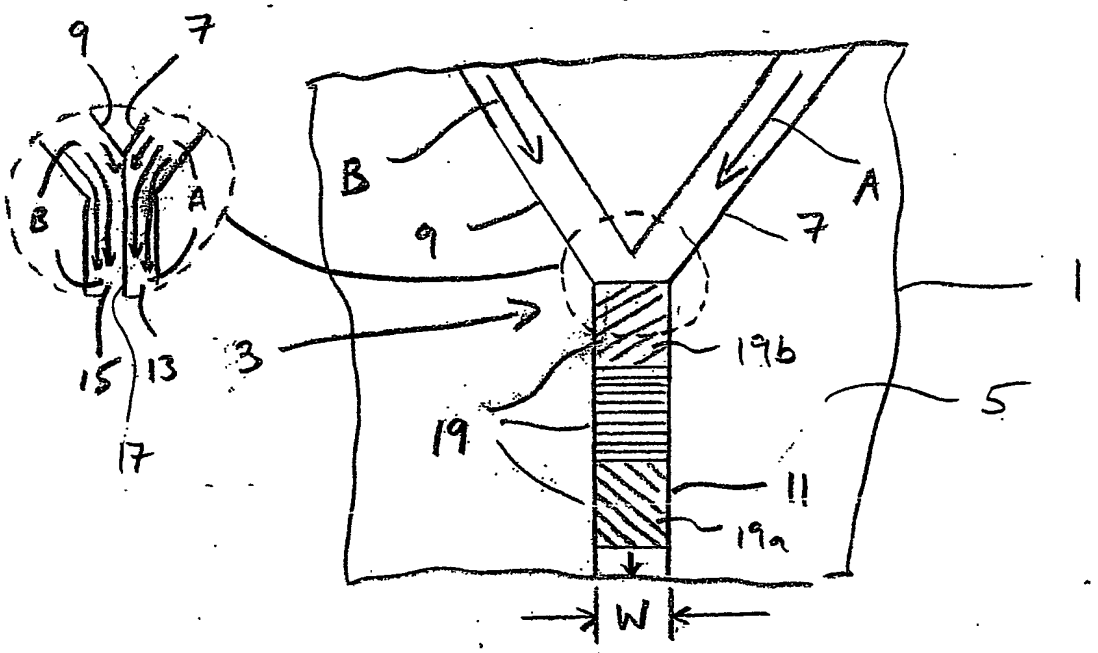
A system (20) comprising a microfluidic chip (1) having a microfluidic channel structure (3;103) in which fluid reagents (A,B;A-C) are flowable to react to produce a reaction product, and an automated closed-loop control mechanism to autonomously control a condition in, or of, the channel structure in accordance with a prescribed regime, the control mechanism having:-

a sensor (27) adapted to produce a sensor signal (29) representative of a predetermined property of the reaction product which is dependent on the condition in, or of, the channel structure,

means (25) adapted to vary the condition in, or of, the channel structure, and

a computer (21) which is programmed with the prescribed regime and adapted to receive the sensor signal and to cause the means to vary the condition in, or of, the channel structure in dependence of the sensor signal.

(FIG. 2)


9
7
B
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19b
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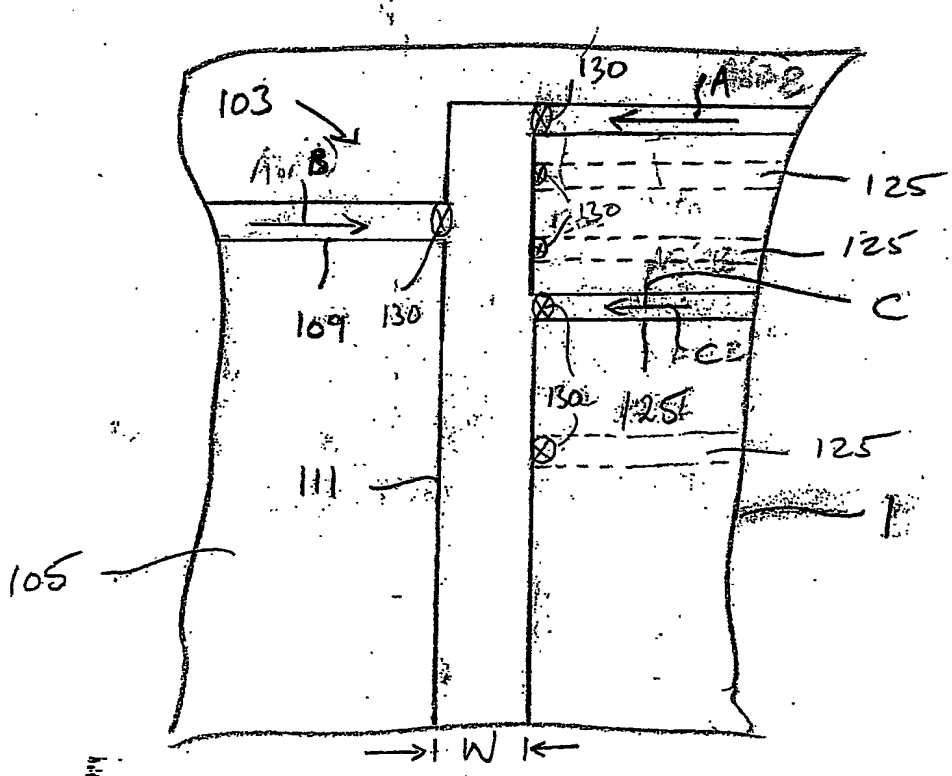
FIG. 1


130
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A or B
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FIG. 3

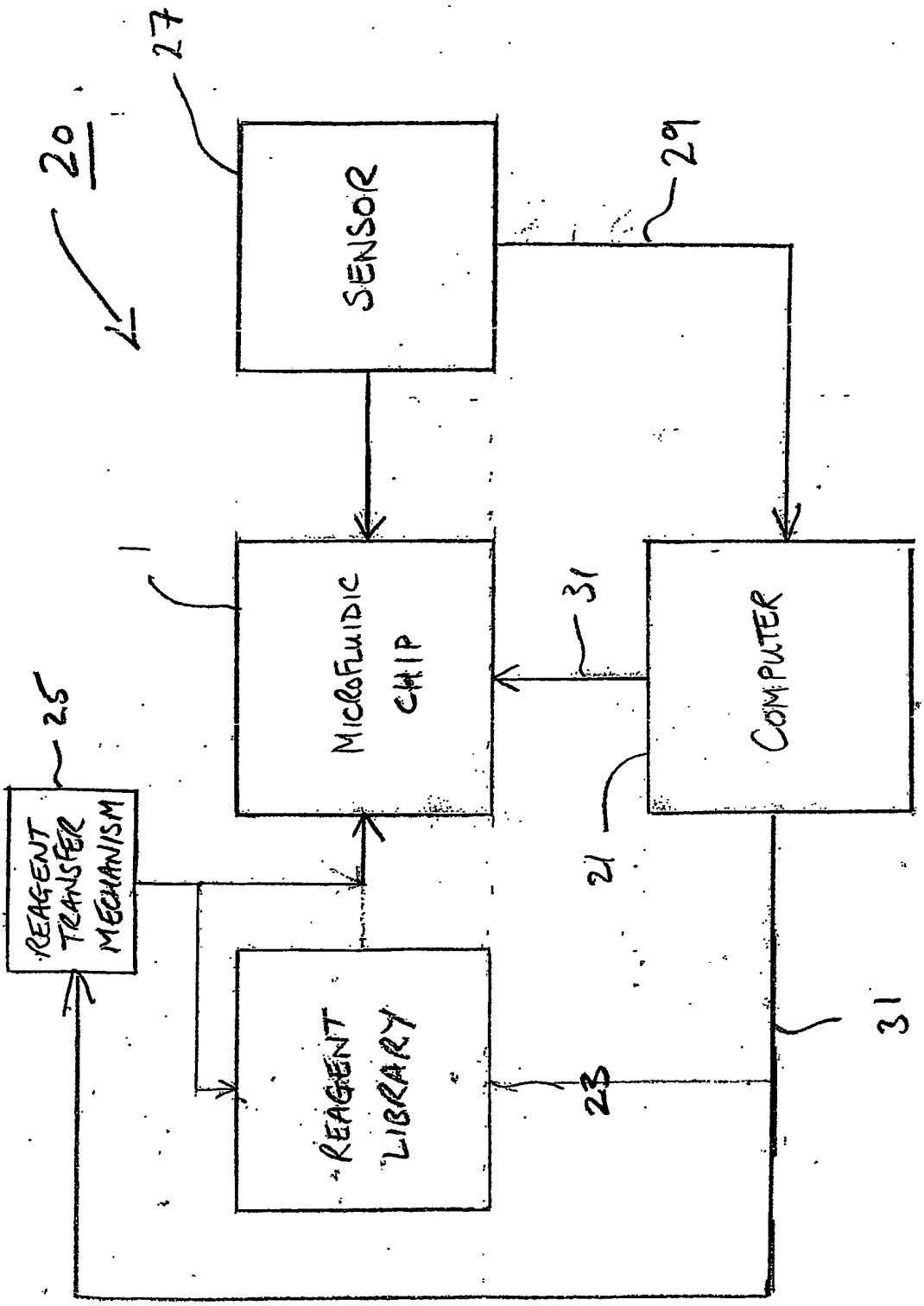
20
27
SENSOR
29
1
MICROFLUIDIC CHIP
31
COMPUTER
25
REAGENT TRANSFER MECHANISM
21
REAGENT LIBRARY
23
31

FIG. 2

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